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Dkt. No.: PP001593.0004
2300-1593

PATENT

CERTIFICATE OF MAILING PURSUANT TO 37 CFR § 1.8

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Appeal Brief, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on **December 5, 2005**.

12/5/05 Michelle Hobson

Date Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	Examiner: B. Li
POLO et al.	Group Art Unit: 1648
Serial No.: 09/551,977	Confirmation No.: 2230
Filing Date: April 14, 2000	Customer No.:
Title: COMPOSITIONS AND METHODS FOR GENERATING AN IMMUNE RESPONSE UTILIZING ALPHAVIRUS-BASED VECTOR SYSTEMS	

TRANSMITTAL LETTER

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Sir:

Transmitted herewith for filing, please find the following documents:

X Reply Brief (12 pgs) with attached Claims Appendix (2 pgs)

X Return receipt postcard

The fee is calculated as follows:

	NO. OF CLAIMS	CLAIMS PREVIOUSLY PAID FOR	EXTRA CLAIMS	RATE	FEE
Total Claims	6	- 37	0	x $50.00	$0
Independent Claims	1	- 9	0	x $200.00	$0
Multiple dependent claims not previously presented, add $360.00					$0
Total Amendment Fee					$0
Petition for Extension of Time Fee					$0
Small Entity Reduction (if applicable)					$0
TOTAL FEE DUE					$0

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 18-1648.

Respectfully submitted,

Date: December 5, 2005

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REPLY BRIEF

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TABLE OF CONTENTS

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REPLY BRIEF

Mail Stop Appeal Brief
Commissioner for Patents
Alexandria, VA 22313

Sir:

Pursuant to Section 41.37(c) (69 Fed. Reg. 49962, Aug 2004), Applicants submit the following Reply Brief in Response to the Examiner's Answer mailed on October 5, 2005. This Reply Brief is submitted within two months of the date of mailing of the Examiner's Answer, namely by December 5, 2005. Appellants respectfully request that the decision of the Examiner be reversed.

STATUS OF THE CLAIMS

Claims 17 and 19-23 are currently pending in the above-referenced case (hereinafter "the application"). The application was originally filed on April 14, 2000 with claims 1-37. In response to a Restriction Requirement (mailed on May 30, 2001), claims 17 and 19-23 were elected, with traverse. Claims 1-16, 18 and 24-37 were canceled, without prejudice or disclaimer, in an Amendment submitted on January 21, 2003. Claim 17 was amended in papers submitted on March 4, 2002, September 4, 2002, January 21, 2003 and July 25, 2003. Claims 19 and 21-23 were amended in the paper submitted on January 21, 2003. Accordingly, claims 17 and 19-23 are pending as shown in the Claims Appendix. Claim 20 is allowable and claims 17, 19 and 21-23 remain rejected under 35 U.S.C. § 112, first paragraph (written description).

GROUNDS OF REJECTION

1. Claims 17, 19 and 21-23 stand rejected under 35 U.S.C. § 112, 1st paragraph as not being adequately described by the specification as filed.

ARGUMENTS

1. The Appeal Brief Contains a Clear Statement About Related Appeals and Interferences

In the Examiner's Answer it was stated that the Appeal brief did "not contain a statement identifying the related appeals and interferences." (Examiner's Answer, page 1). In fact, the Appeal Brief contains both a statement that Appellants are not aware of any related appeals or interferences AND an appendix reiterating this (see Appeal Brief, page 2 and Appendix).

2. The Specification Describes the *Claimed* Subject Matter

Appellants incorporate herein all the arguments set forth in their Appeal Brief. Rather than reiterate each argument herein, Appellants address various assertions set forth in the Examiner's Answer, in which it was again maintained that the specification as filed does not adequately describe claims 17, 19 and 21-23. In particular, the Examiner raised the following points:

- Alphaviruses are known and well-characterized, particularly with respect to the fact that all alphaviruses contain the E2 protein. (Examiner's Answer, pages 3-4 and 6-7)
- Alphaviruses are not identical in size and some may contain a third envelope protein, allegedly indicating that there is "substantial variation" as between alphaviruses. (Examiner's Answer, page 4)
- Procedures of making E2 mutations and assaying dendritic cell (DC) infectivity of these mutants are well known in the art. (Examiner's Answer, page 4)
- The fact that no one else has published on Appellant's invention is "evidence" of lack of description in the specification as filed. (Examiner's Answer, page 4)
- The claims, drawn to mutants of E2 having a mutation in a 5 amino acid large region, are "broad" in scope. (Examiner's Answer, page 4)

- Appellants must exemplify (reduce to practice) multiple different alphaviruses having a mutation between the claimed 158 to 162 residues and which are DC-tropic. (Examiner's Answer, page 5)

The written description requirement implements the principle that a patent must describe the technology that is sought to be patented. To comply with the written description requirement, each claim limitation must be expressly, implicitly or inherently supported in the originally filed disclosure.

Appellants' claimed invention relates to recombinant alphavirus particles comprising an alphavirus replicon and an amino acid mutation in its E2 glycoprotein, wherein the mutation is in the region corresponding to amino acids 158-162, numbered relative to wildtype SIN E2 glycoprotein, wherein the particle is capable of infecting human dendritic cells, with the proviso that the particle is not derived from ATCC # VR-2526.

The specification discloses recombinant alphavirus particles which infect human dendritic cells, with the proviso that the particle is not derived from ATCC # VR-2526 (see, e.g., originally filed claim 17). The specification discloses that, in certain embodiments, the recombinant alphavirus particles have an amino acid substitution in the E2 glycoprotein as compared to wildtype, for example, at residue 158, 159, 160, 161 or 162 (see, e.g., page 5, lines 4-6). The specification discloses that, in other embodiments, the recombinant alphavirus particles have an amino acid deletion or insertion in the E2 glycoprotein (see, e.g., page 5, lines 7-8). The specification further discloses that the alphavirus can be a Semliki Forest virus, a Ross River virus, a Venezuelan equine encephalitis virus or a Sindbis virus (see, e.g., page 5, lines 9-10 and originally filed claims 19 and 21-23). The specification also discloses that recombinant alphavirus particles contain an alphavirus RNA replicon comprising a heterologous sequence (see, e.g., page 15, lines 13-18). Thus, each claim limitation is expressly supported in the

originally filed disclosure. Accordingly, the specification sufficiently describes the claimed invention and Appellants have satisfied the written description requirement.

Appellants also address various other points made by the Examiner in the Examiner's Answer.

First, it is irrelevant to claims relating to E2 that some alphaviruses contain a third (E3) protein. The claimed invention relates to recombinant alphavirus particles comprising an amino mutation in its E2 glycoprotein. Glycoprotein E2, as acknowledged by the Examiner, is included in every single alphavirus isolate. *See, e.g.,* pages 4-7 of Examiner's Answer. The Examiner also acknowledges that alignment of proteins and assays for DC infectivity are described and/or well known. *Id.* Written description is determined with respect to the claimed invention, in this case recombinant alphavirus particles comprising an amino acid mutation in its E2 glycoprotein, wherein the particle is capable of infecting human dendritic cells. The presence or absence of E3 is irrelevant to the present written description inquiry. All that is required to show that Appellants had possession of the claimed invention at the time the present application was filed is a description in the specification of the claimed subject matter in sufficient detail that a skilled artisan can reasonably conclude that Appellants had possession of the claimed invention at the time the present application was filed. As discussed above and in the Appeal Brief, the specification sufficiently describes the claimed invention and, accordingly, the written description requirement is satisfied.

Secondly, it is irrelevant to a written description inquiry that there are no publications regarding E2 mutants and DC-tropism. Appellants have provided a specification that does not require supplementation by publications. Rather, the specification as filed satisfies the requirements of 35 U.S.C. § 112, first paragraph.

Furthermore, because the specification contains a literal description of the claimed subject matter, the Examiner errs in contending that "all species of the claimed mutated alphavirus genus" must be reduced to practice (*i.e.,* exemplified) in order to evince possession.

See, e.g., pages 5 and 9 of the Examiner's Answer. Exemplification of each and every possible embodiment is not a requirement of 35 U.S.C. § 112, first paragraph and, in fact, the Federal Circuit, the Board, the M.P.E.P. and the PTO's own Training Materials forbid such a test.

With regard to the various cases cited in the Examiner's Answer, Appellants submit that a written description inquiry is fact-dependentand that the holdings in the various cases cited in the Answer are particular to the facts of those cases. In fact, the specification at issue in every case cited by the Examiner did not contain a literal description of the claimed subject matter. In contrast, Appellants' specification contains express support for the claimed invention and, accordingly, possession of the invention at the time the application was filed has been established.

The cases cited by the Examiner also affirm the well-established rule that an applicant need not describe that which is not new. As set forth in *Capon v. Eshhar* 76 USPQ2d 1078 (Fed. Cir. 2005), the Federal Circuit rejected the notion that the specification must describe information (*e.g.,* sequence data) that is either known or can readily be determined based on scientific facts (*Capon* at page 15, emphasis added):

> The "written description" requirement must be applied in the context of the particular invention and the state of the knowledge. The Board's rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization. ...
>
> The "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution.

As in *Capon*, the Examiner's assertion in the instant case that Appellants are required to disclose particular mutations in each and every alphavirus species described in the specification, when the E2 sequences of these (and other alphaviruses) were well known and could be readily aligned with the prototype SIN to determine residues corresponding to 158-162, is inappropriate.

Appellants have already identified the structure-function correlation by pointing to a region of 5 amino acids that is mutated and by reciting that the mutated molecule must have DC infectivity.

Moreover, the Examiner admits that it was well known that (1) all alphaviruses contain E2; (2) alphavirus E2 proteins were well characterized; (3) aligning amino acid sequences was routine (and literally described by the specification as filed with respect to alphaviruses, for example on page 37); and (4) assaying for the claimed function limitation was well known (and literally described by the specification as filed). Combined with the express disclosure of the 5 particular amino acids subject to mutation, the skilled artisan would have recognized that Appellants were in possession of the claimed genus of recombinant alphavirus particles at the time the present application was filed.

Finally, in regard to the Examiner's assertions with regard to Dr. Polo's Declaration, particularly that "appellants ... ignored the written description rejection" and that "appellants did not ask the examiner to consider the Declaration prior to the current appeal brief" (Examiner's Answer, page 11), Appellants respectfully disagree with the Examiner's characterizations. Appellants clearly addressed the written description rejection and referred to Dr. Polo's Declaration when the Examiner initially raised written description as an issue (*see,* Appellants' Response filed September 2, 2004, pages 2-3, emphasis added):

> In addition, claims 21-23 were also rejected under 35 U.S.C. § 112, first paragraph as allegedly not described in the specification as filed. (Office Action, paragraphs 12-14). Again, it was maintained that the specification does not adequately describe mutations other than that at position 160. *Id.* ...
>
> On July 27, 2003, Applicants responded to these rejections and, in addition, submitted a Declaration under 37 C.F.R. § 1.132 by John Polo addressing these very points. ...
>
> For the reasons of record, **including the declaratory evidence** previously submitted and found persuasive, Applicants submit that the Office has already deemed the specification as filed to be fully enabling **and to adequately describe the subject matter of all the pending claims**. Accordingly, the rejection should be withdrawn.

Appellants submit that all evidence (including Declaratory evidence) must be considered in its entirety. As set forth in the Appeal Brief, Dr. Polo's Declaration directly addresses written description issues, for example in paragraphs 7, 8 and 11, emphasis added:

> 7. When the specification was filed, it clearly taught a typical scientist how to make and use recombinant alphavirus particles from a variety of alphavirus species, where the particles are capable of infecting human dendritic cells and contain an amino acid mutation at positions 158-162 (based on SIN numbering) of E2 (relative to the wild-type alphavirus source). **Thus, I believe that a typical scientist would have understood the specification clearly described all of the various aspects of the claims** and enabled a typical scientist to make and use the invention as set forth in the pending claims. I base this belief on the facts set forth below.
>
> 8. ... In view of the teachings of the specification, it would have been routine for the skilled artisan to align and compare nucleotide and amino acid sequences from various alphaviruses and determine which amino acid sequences in any alphavirus corresponded to positions 158-162 of a SIN E2 protein. (See, *e.g.*, page 37 of the specification, **describing** alignment of SIN strains). Also, in view of the **disclosure**, a person of skill in the art would surmise that mutants in this region would be much more likely to exhibit DC-tropism. Accordingly, it is my opinion that using the teachings of the specification and state of the art, it would require only routine experimentation for a typical scientist to obtain suitable amino acid sequences from any alphavirus (for example by comparison with sequences disclosed in the specification) and use these alphavirus sequences as a starting point for making the claimed particles.
>
> 11. Fourth, it would have been clear to a typical scientist how to test for the ability of a mutant alphavirus particle falling within the scope of the claims to infect human dendritic cells. (See, *e.g.*, page 42 of the specification). Methods of culturing human dendritic cells were **known and described** in the specification as filed. (See, *e.g.*, Example 1). Moreover, methods of testing the ability of alphavirus particle to infect these cells **are described** in detail in the specification and include, but are not limited to, testing FACS analysis, titer analysis, use of reporter molecules, and the like. (See, *e.g.*, page 40; page 42-43). Thus, it is my opinion that a typical scientist could have readily tested any recombinant

alphavirus particle containing the claimed mutation, following the teachings of the specification.

Thus, the Examiner errs in asserting that Appellants ignored the written description rejection. The Examiner further errs in asserting that Dr. Polo's Declaration did not address written description and that Appellants did not point out the relevance of his Declaration until the Appeal Brief.

In summary, for the reasons of record as set forth herein and in the Appeal Brief, the written description rejection cannot stand. Each claim limitation is expressly supported in the originally filed disclosure. Thus, a person skilled in the art would recognize that Appellants were in possession of the claimed genus of recombinant alphavirus particles at the time the present application was filed. Accordingly, the specification sufficiently describes the claimed invention and Appellants have satisfied the written description requirement.

The Examiner has the initial burden of presenting evidence or reasoning to explain why persons skilled in the art would not recognize in the original disclosure a description of the invention defined by the claims. Appellants respectfully submit that this burden has not been met.

CONCLUSION

For the reasons stated above, Appellants respectfully submit that the pending claims are described by the specification as filed. Accordingly, Appellants request that the rejection of the claims on appeal be reversed, and that the application be remanded to the Examiner so that the appealed claims can proceed to allowance.

Respectfully submitted,

Date: December 5, 2005

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CLAIMS INVOLVED IN THE APPEAL

1 to 16. (canceled).

17. (previously presented): A recombinant alphavirus particle comprising

an alphavirus replicon comprising a heterologous sequence; and

an amino acid mutation in its E2 glycoprotein, wherein the mutation in the E2 glycoprotein is in the region corresponding to amino acids 158 - 162, numbered relative to wild-type SIN E2 glycoprotein, and further wherein said particle is capable of infecting human dendritic cells, with the proviso that said recombinant alphavirus particle is not derived from ATCC # VR-2526.

18. (canceled).

19. (previously presented): The recombinant alphavirus particle of claim 17 wherein said alphavirus is a Sindbis virus.

20. (original): The recombinant alphavirus particle according to claim 19 wherein said alphavirus has an amino acid substitution at E2 residue 160, as compared to wild-type Sindbis virus.

21. (previously presented): The recombinant alphavirus particle according to claim 17 wherein said alphavirus is Semliki Forest virus.

22. (previously presented): The recombinant alphavirus particle according to claim 17 wherein said alphavirus is Ross River virus.

23. (previously presented): The recombinant alphavirus particle according to claim 17 wherein said alphavirus is Venezuelan equine encephalitis virus.

24 to 37. (canceled).